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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,094	03/14/2001	Christen M. Anderson	660088.420D4	1063

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,094	ANDERSON ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-26 and 30-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-26 and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election of Group III, claims 1-4, 7-26, and 29-41 in the Response filed December 4, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Thus, the restriction requirement is FINAL.

Status of the Claims

Claims 5-7, 27-29, and 42-112 have been cancelled. Claims 1-4, 8-26, and 30-41are pending and will be examined on the merits in this Office Action.

Rejections/Objections Withdrawn

Objection Withdrawn for Specification not in Sequence Compliance

The objection to the Specification for lack of sequence identifiers for the sequences in Figures 1A, 1B, and 2 is withdrawn in light of the amendment to the Brief Description of the drawings.

Claim Rejections - 35 USC § 112--Withdrawn

Claims 4, 20-26, 30-38, and 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of Claims 36 and 37 under 35 U.S.C. 112, second paragraph is withdrawn in light of the amendment changing the dependency of the claims.

The rejection of Claims 4, 20, 26, and 40 (and dependent claims 21-25, 30-38, and 41) under 35 U.S.C. 112, second paragraph for lacking clarity in the metes and bounds of the claims due to the lack of definition as to what recombinant ANT sequences are considered an "animal" or "human" is withdrawn in light of the amendment to the claims.

Claim Rejections - 35 USC § 103--Withdrawn

The rejection of Claims 1-4, 8-17, 20-26, 30-35, and 38-41 under 35 U.S.C. 103(a) as being unpatentable over Krief et al. (U.S. Patent No. 6,316,219; filed 09/1998) in view of Ausubel et al. ((Short Protocols in Molecular Biology, 3rd Ed. (1997) John Wiley & Sons, New York, Chapter 13, pp. 26-35 and Chapter 16, pp. 1-7,16 –23m 25-31, 37-54, 58-62) is withdrawn in light of the amendment to the claim, applicant's arguments, the Anderson Declaration and newly cited references; Hatanaka et al. (Biol. Pharm. Bull. (2001) 24(6): 595-599) and Heimpel et al. (J. Biol. Chem. (2001) 276(15): 11499-11506). Krief et al. and Ausubel et al. do not teach an expression construct comprising a nucleic acid sequence encoding a polypeptide at least 95% identical to SEQ ID NO:33; therefore the references do not teach all of the limitations of the claims as amended. While sequences encompassed by the present claims were well known prior to the date of filing of the present application, the Anderson Declaration, through the Fiermonte et al. reference discussed therein, provides some evidence of difficulties in

ANT expression at the time of the invention. Moreover, Hatanaka et al. teach that in order to achieve successful and significant expression in yeast, the N-terminal region of the human ANT polypeptide had to be replaced with the yeast sequence. Therefore, Hatanaka et al. provide evidence that one of ordinary skill in the art would not have achieved success by combining the teachings of Krief et al. , Ausubel et al. and a reference teaching the sequence of a human ANT3 polypeptide. In addition, Heimpel et al. disclose the expression of an ANT from N. crassa in E. coli. Heimpel et al. state that yeast AAC2 and mammalian AAC (also referred to as ANT) are not expressed at significant levels in E. coli and that there is no evidence that the proteins are incorporated into E. coli membranes (p. 11504, Col. 1). Heimpel et al. also discuss the "challenge" of reconstitution of AAC from inclusion bodies and the modification they had to make for successful reconstitution from inclusion bodies (p. 11504, Col. 2). Thus, Heimpel et al. provides additional evidence of failure to express ANT in E. coli. While both Hatanaka et al. and Heimpel et al. are post-filing references, they show that even after the filing date of the present invention, heterologous expression of ANT is not routine.

The rejection of Claims 7 and 29 under 35 U.S.C. 103(a) as being unpatentable over Krief et al. and Ausubel et al. as applied to claim1-4, 8-17, 20-26, 30-35, and 38-41 above, and further in view of Cozens et al. (J. Mol. Biol. (1989) 206: 261-280; ref. BF of IDS of Paper No. 5) is withdrawn for the same reasons as given above.

The rejection of Claims 18, 19, and 36-37 under 35 U.S.C. 103(a) as being unpatentable over Krief et al. and Ausubel et al. as applied to claims 1-4, 8-17, 20-26,

30-35, and 38-41 above, and further in view of Le Saux et al. (Biochemistry (1996) 35: 16116-16124) and Wallace et al. (WO 98/19714,; Ref. AE of IDS of Paper No. 5) is withdrawn for the same reasons as above.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8-26, and 30-41 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for a recombinant expression construct encoding a fusion protein comprising at least one promoter operably linked to a nucleic acid molecule comprising a first nucleic acid molecule encoding a first polypeptide and a second nucleic acid molecule encoding an adenine nucleotide translocator 3 (ANT3) polypeptide having at least 95% identity to an ANT3 polypeptide comprising the sequence of SEQ ID NO:33, wherein the expression construct expresses a fusion protein with the first polypeptide fused to the N-terminus of the ANT3 polypeptide, as well as host cells containing such expression constructs and methods of making ANT polypeptides using such constructs. However, the Specification does not reasonably provide enablement for expression constructs (or host cells containing them or methods of using them) that do not express the ANT polypeptides as fusion proteins with an N-terminal polypeptide sequence. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation would be required to develop recombinant expression of non-fusion ANT polypeptides having the claimed sequences that would be active and useful. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Nature of the Invention and Breadth of the Claims includes recombinant expression of unmodified ANT polypeptides:

The Specification indicates that the invention relates to the recombinant production of ANT polypeptides (p. 1, lines 7-10). The Anderson Declaration filed December 4, 2003, indicates that the present invention solves a long felt, unmet need for recombinant human ANT3 polypeptides. The claimed invention involves recombinant expression constructs (as well as host cells containing the constructs and methods of making polypeptides using the constructs) that encode polypeptides having at least 95% identity to SEQ ID NO:33 or polypeptides having at least 95% identity to SEQ ID NO:33 that are expressed as fusion proteins with a polypeptide of a second nucleic acid sequence wherein the second polypeptide can be fused to any part of the

first polypeptide. Thus, the breadth of the claims encompasses expression constructs that would express ANT3 alone and those that would express ANT3 as a fusion protein.

State of the prior art and relative skill of those in the art-- expression of active ANT unsuccessful without modification of ANT sequence:

The Anderson Declaration filed November 7, 2003 provides evidence of the relative skill and state of the prior art. Fiermonte et al. (Biochem. J. (1993) 294: 293-299) (discussed in the Anderson Declaration) teach that attempts to recombinantly express ANT in E. coli did not result in detectable levels of mammalian ANT polypeptides. In addition, the post-filing reference of Heimpel et al. (J. Biol. Chem. (2001) 276(15): 11499-11506) provides evidence that that those of skill in the art even at the time and after the filing date of the present invention did not know how to express a functional ANT in E. coli. Heimpel et al. state that attempts to express human ANT1 in E. coli were unsuccessful and evidence of ANT membrane expression in the E. coli was not found (p. 11504, Col. 1, 2nd paragraph). Miroux et al. (J. Mol. Biol. (1996) 260(3): 289-298)(discussed in the Anderson Declaration) successfully expresses recombinant ANT in E. coli, however, it appears that the expressed ANT accumulates in inclusion bodies where it is unfolded and inactive. Hatanaka et al. (Biol. Pharm. Bull. (2001) 24(6): 595-599) discloses that in order to get successful expression of human ANT1 in yeast, the first 11 residues of the human N-terminal sequence had to be replaced with the corresponding 26 residues of the yeast AAC2 (see p. 597, Col. 1). Such a modification would make the human ANT1 less than 95% identical to ANT1 of SEQ ID NO: 31. Therefore, as a whole it appears that the state of the art and those of

skill in the art did not know of a method that would successfully express an active ANT (one that would be able to bind) in E. coli and did not know of a method to express an active ANT in yeast without some type of modification of the N-terminal sequence.

Direction/Guidance and working examples only describe expression of ANT fusion proteins with additional polypeptide sequence N-terminal to the ANT sequence:

The present Specification only describes and provides examples for successful expression of ANT polypeptides fused at the N-terminus to a his-tag sequence (containing 6 histidines at the N-terminus of ANT sequence) or GST (Glutathione-S-transferase) in various cell types. The Specification does not provide any examples or guidance of expressing ANT polypeptides without fusion of an additional sequence to the N-terminus.

Expression of non-fusion ANT polypeptides highly Unpredictable:

Given the difficulties and lack of success in the prior art and the lack of guidance or examples in the present Specification discussed above and the lack of knowledge of the source of the problem in ANT expression, determination of what method steps would be required to successfully express the claimed ANT polypeptides without an N-terminal fusion is highly unpredictable.

Undue Experimentation would be required:

To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the discovery of a method that would allow successful recombinant

expression of an unmodified and active ANT or ANT fusion wherein the fused polypeptide is not located at the N-terminus. Such a discovery would constitute undue experimentation. Thus, for the reasons described above, the full scope of the claims is not considered enabled.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
February 17, 2004

Christopher S. F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600